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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/724,292	12/01/2003	Juan Armendariz Borunda	5585-036-999	4513

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EXAMINER	
CHEN, SHIN LIN	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 11/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/724,292	ARMENDARIZ BORUNDA ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2003 and 08 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7-19-04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' preliminary amendments filed 12-1-03 and 4-8-04 have been entered. Claims 1-21 have been canceled. Claims 22-27 have been added. Claims 22-27 are pending and under consideration.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Mexico on 9-17-99. It is noted, however, that applicant has not filed a certified copy of the Mexico 998515 application as required by 35 U.S.C. 119(b).

Specification

1. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to **a single paragraph on a separate sheet within the range of 50 to 150 words**. It is important that the abstract **not exceed 150 words in length** since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

The abstract on page 32 of the specification contains more than one paragraph and exceeds 150 words. The abstract should be in a single paragraph and shall not exceed 150 words. Appropriate correction is required.

2. The amendment filed 12-1-03 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The amendment filed 12-1-03 amends the

specification by inserting after the title on page 1 "This application is a divisional of U.S. application no. 10/098,359, filed March 18, 2002, ...**the disclosures of which are incorporated herein by reference**". The added material which is not supported by the original disclosure is as follows: The oath/ declaration only claims priorities of parent applications but fails to incorporate herein by reference. Thus, the amendment filed 12-1-03 introduces new matter into the specification.

Applicant is required to cancel the new matter in the reply to this Office Action.

The term "CLAIMS" on page 29 of the specification is improper. Changing the term "CLAIMS" to "We claim:" or "What is claimed is:" would be remedial.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 22 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "unitary doses of viral particles" in claim 22 is vague and renders the claim indefinite. The term "unitary" means "of or relating to a unit" or "having the character of a unit" according to the Merrian-Webster OnLine Dictionary. However, it is unclear as to the metes and bounds of what would be considered "unitary doses". It is unclear how many viral particles is

considered "unitary dose". The specification fails to specifically define the phrase "unitary doses of viral particles".

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 22-27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 22-27 are directed to a pharmaceutical composition comprising a therapeutically effective amount of unitary doses of viral particles of recombinant adenoviral vectors containing a therapeutic gene or DNA sequence under the control of a ubiquitous promoter, a tissue-specific promoter or a combination thereof, for the treatment of fibrotic disorders in organs and a pharmaceutically acceptable carrier, and a method of treating fibrotic disorders, such as hepatic fibrosis, pulmonary fibrosis, renal fibrosis, keloids, hypertrophic scars, or combination thereof, in a patient by delivering a recombinant adenoviral vector expressing therapeutic proteins via an administration route to an organ. Claim 23 specifies the unitary dose is about 10^7-10^{14} viral particles. Claim 25 specifies the administration route is endovenous.

The specification discloses that the rat models, including healthy rats, rats intoxicated with carbon tetrachloride (CCl4) and rats with ligation of the bile duct (LCB), receive infusion of

Ad5gal vector by iliac vein shows that the main target organ of the infused adenoviral vector is the liver. The spleen and the lung present a transduction grade lower than 1% and other organs, such as kidney, heart and brain, show no transduction at all (specification, pages 12-16).

The specification states "[t]he present invention relates to the creation of RECOMBINANT ADENOVIRAL vectors bearing exogenous genes that encodes for therapeutic proteins useful in the treatment of HEPATIC cirrhosis and generalized FIBROSIS, such as renal FIBROSIS, pulmonary FIBROSIS, HYPERTROPHIC scars and keloid of the skin, and/or in other target organs susceptible to suffer from it" and "the invention provides an effective way for the treatment of fibrosis through the employment of recombinant adenoviral vectors which are claimed here, as well as the process to prepare these vectors, the pharmaceutical composition that contains them, and their therapeutic uses in the treatment of several fibrosis" (specification, page 1, first and second paragraphs). The "pharmaceutical composition" implies therapeutic use of said composition. Thus, the claims read on gene therapy for the treatment of various fibrotic diseases or disorders in vivo.

The claims encompass treating various fibrotic diseases or disorders in a patient by delivering a recombinant adenoviral vector expressing any therapeutic protein under the control of a promoter via various administration routes in vivo. The specification fails to provide adequate guidance and evidence for delivering a recombinant adenoviral vector expressing any therapeutic protein under the control of a promoter via various administration routes in vivo such that therapeutic effects can be obtained so as to treat any fibrotic disease or disorder in a patient.

The claims read on gene transfer and gene therapy in vivo. The nature of the invention being gene therapy, the state of the prior art was not well developed and was highly

unpredictable at the time of filing. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, Deonarain, M., 1998 (Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Verma et al., Sept. 1997 (Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector.. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Verma states that "The Achilles heel of gene therapy is gene delivery, and this is the aspect that we will concentrate on here. Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression...The use of viruses (viral vectors) is powerful technique, because many of them have evolved a specific machinery to deliver DNA to cells, However, humans have an immune system to fight off the virus, and our attempts to deliver genes in viral vectors have been confronted by these host responses." (e.g. p. 239, column 3). The adenoviral vector can induce both cell-killing "cellular" immune response and the antibody-producing "humoral" immune response from the host. The virally infected cells can be killed by cytotoxic T lymphocytes and the humoral response results in the generation of antibodies against adenoviral proteins. "There are considerable

immunological problems to be overcome before adenoviral vectors can be used to deliver genes and produce sustained expression" (e.g. p. 241, left and middle column).

Eck et al., 1996 (Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, p. 77-101) states that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced are all important factors for a successful gene therapy (e.g. bridging pages 81-82). In addition, Gorecki, 2001 (Expert Opin. Emerging Drugs, 6(2): 187-198) reports that "the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression" for gene therapy, and obstacles to gene therapy *in vivo* include "the development of effective clinical products" and "the low levels and stability of expression and immune responses to vectors and/or gene products" (e.g. abstract). Thus, administration route plays an important role in gene transfer efficiency.

Further, the administration route includes oral administration, intraperitoneal injection, topical administration, intravenous administration, intramuscular injection, and subcutaneous administration etc. As discussed above, the specification discloses that infusion of Ad5gal vector into rats by iliac vein shows that the main target organ of the infused adenoviral vector is the liver. Other organs, such as spleen, lung, kidney, heart and brain, show either very low transduction efficiency or no transduction at all. It appears that when an adenoviral vector is

administered via infusion or intravenous administration, most of the adenoviral vector reaches the liver but very little reaches other organs. The specification fails to provide adequate guidance and evidence for whether intravenous (endovenous) administration of an adenoviral vector to a patient could provide sufficient expression of a therapeutic protein in any organ other than the liver in said patient so as to provide therapeutic effect for treating various fibrotic disorders in different organs. The specification also fails to provide adequate guidance and evidence for whether various administration routes of an adenoviral vector to a patient could provide sufficient expression of a therapeutic protein in any organ, including the liver, in said patient so as to provide therapeutic effect for treating various fibrotic disorders in different organs. There is no evidence of record that shows administration of a recombinant adenoviral vector expressing a therapeutic protein under the control of a promoter into a patient via various administration routes can provide therapeutic effects for treating various fibrotic disorders or diseases in said patient. Therefore, one skilled in the art would not know how to use the recombinant adenoviral vector for treating various fibrotic diseases or disorders via various administration routes in vivo.

The claims also encompass using nucleotide sequences encoding various therapeutic proteins for treating various fibrotic diseases or disorders in a patient. However, different therapeutic proteins have different amino acid sequences and their biological functions would differ. It was known in the art that the amino acid sequence of a protein determines its structural and functional properties, and predictability of which amino acids can be removed from a protein's sequence and still result in similar activity is extremely complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's structure from mere

sequence data are limited. Rudinger, 1976 (Peptide Hormones, Edited by Parsons, University Park Press, Baltimore, p. 1-7), points out that "The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study" (e.g. p. 6). Kaye et al., 1990 (Proc. Natl. Acad. Sci. USA, Vol. 87, pp. 6922-6926) teaches that "A single amino acid substitution results in a retinoblastoma protein defective in phosphorylation and oncoprotein binding" (e.g. Title). Davis, C. G., 1990 (The New Biologist, Vol. 2, No. 5, p. 410-419) reports that EGF repeats appears in an extraordinarily diverse group of molecules, including growth factors, transmembrane molecules, extracellular matrix proteins, and soluble secreted proteins, and it is often difficult to deduce what contribution the EGF repeat makes in a totally unrelated protein (e.g. p. 410, left column). It appears that EGF repeat can contribute to different biological functions in different amino acid contexts, i.e. different proteins.

Further, Skolnick et al., 2000 (Trends in Biotech, Vol. 18, p. 34-39) states "Sequence-based methods for function prediction are inadequate because of the multifunctional nature of proteins. However, just knowing the structure of the protein is also insufficient for prediction of multiple functional sites. Structural descriptors for protein functional sites are crucial for unlocking the secrets in both the sequence and structural-genomics projects" (e.g. abstract). Skolnick further states that "Knowing a protein's structure does not necessarily tell you its function" and "Because proteins can have similar folds but different functions, determining the structure of a protein may or may not tell you something about its function" (e.g. p. 36, box 2). Therefore, biological function of a protein was unpredictable from mere amino acid sequence at

the time of the invention and even same short stretch of amino acid sequence can show diverse biological functions while surrounded by different background amino acid sequences.

In view of the unpredictable nature of gene therapy in vivo, the limitation of using adenoviral vectors in gene delivery, and the unpredictable biological function of a protein from mere amino acid sequence, one skilled in the art at the time of the invention would not know how to use the recombinant adenoviral vector expressing any therapeutic protein for treating various fibrotic diseases or disorders via various administration routes in vivo. One of skilled in the art would require to identify and characterize the nucleotide sequence of the therapeutic protein, trial and error experimentation to determine the biological function of various therapeutic proteins, preparation of adenoviral vectors expressing various therapeutic proteins, administration of said viral vectors into a subject via various administration routes, trial and error experimentation to determine whether sufficient therapeutic protein is expressed at the target organ via various administration routes, and trial and error experimentation to determine whether the expressed therapeutic protein can provide therapeutic effect for treating various fibrotic diseases or disorders in vivo.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the level of ordinary skill which is high, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 22 and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Hattori et al., January 1999 (Human Gene Therapy, Vol. 10, no. 2, pp. 215-222).

Claims 22 and 23 are directed to a pharmaceutical composition comprising a therapeutically effective amount of unitary doses of viral particles of recombinant adenoviral vectors containing a therapeutic gene or DNA sequence under the control of a ubiquitous promoter, a tissue-specific promoter or a combination thereof, for the treatment of fibrotic disorders in organs and a pharmaceutically acceptable carrier. Claim 23 specifies the unitary dose is about 10^7-10^{14} viral particles.

Hattori teaches generation of recombinant adenoviruses containing human and mouse urokinase-type plasminogen activator (uPA) cDNA under the control of CMV promoter. A single intratracheal instillation of these uPA-containing adenoviruses into mouse lungs resulted in increased plasminogen activator activity in bronchoalveolar lavage fluid and the A549 cells infected with the adenoviruses can lyse plasma-derived fibrin-rich matrices in vitro (e.g. abstract, p. 216, left column). Hattori teaches a single intratracheal instillation of 2.5×10^8 PFU of virus into mice results in greater PA activity as compared to control (e.g. p. 218, left column). The uPA gene encodes a therapeutic protein for treating the fibrotic disorders in organs. The dose of

2.5×10^8 PFU of the adenovirus falls within the range of 10^7-10^{14} viral particles. Thus, claims 22 and 23 are anticipated by Hattori.

It should be noted that the term "pharmaceutical" is the intended use of the claimed composition, therefore, it does not carry weight in the 35 U.S.C. 102(b) rejection.

9. Claim 22 is rejected under 35 U.S.C. 102(b) as being anticipated by Jaffe et al., April-May 1999 (Experimental Lung Research, Vol. 25, No. 3, pp. 199-215).

Claim 22 is directed to a pharmaceutical composition comprising a therapeutically effective amount of unitary doses of viral particles of recombinant adenoviral vectors containing a therapeutic gene or DNA sequence under the control of a ubiquitous promoter, a tissue-specific promoter or a combination thereof, for the treatment of fibrotic disorders in organs and a pharmaceutically acceptable carrier.

Jaffe teaches that interferon-gamma (IFN-gamma) inhibits the fibrotic process by direct effect on collagen synthesis and by suppressing the induction of TGF-beta gene, whose product stimulates collagen gene expression (e.g. p. 200). Jaffe teaches generation of a replication-deficient recombinant adenovirus, AdCMVmIFNgamma, expressing mouse IFN-gamma protein under the control of CMV promoter for gene transduction in vitro (e.g. p. 201-202). The IFN-gamma gene encodes a therapeutic protein for treating the fibrotic disorders in organs. Thus, claim 22 is anticipated by Jaffe.

It should be noted that the term "pharmaceutical" is the intended use of the claimed composition, therefore, it does not carry weight in the 35 U.S.C. 102(b) rejection.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Shin-Lin Chen, Ph.D.

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